Quetiapine Induced Neuroleptic Malignant Syndrome

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Abstract
A case of quetiapine-induced neuroleptic malignant syndrome is presented. A 21-year-old gentleman with paranoid schizophrenia developed fever, muscle rigidity autonomic lability, clouding of consciousness and increased creatine kinase two weeks after change of neuroleptic medication. The clinical symptoms resolved one week after discontinuation of the newer neuroleptic medication.

Key words: quetiapine; neuroleptic malignant syndrome

Introduction
Neuroleptic malignant syndrome (NMS) was first described by Delay in 1968 (Delay 1968). It is an uncommon but serious consequence related to agents that affect dopamine neurotransmission (Levenson 1985). Quetiapine is a relatively new antipsychotic drug that has only low affinity for dopamine receptors but with higher potency towards adrenergic receptors. Due to its characteristic pharmacokinetic properties, it is expected that NMS is not a common complication of quetiapine prescription. We should pay attention to this rare but potentially fatal complication since there is escalating use of newer antipsychotic drugs in recent years related to their favourable side effect profile compared to traditional antipsychotic medication. We present a case of NMS related to quetiapine therapy in a patient with paranoid schizophrenia.

Case Report
A 21-year-old gentleman with history of mild mental retardation was admitted to mental hospital because of mental deterioration. He presented with agitation, and increase in irritability. He harboured auditory hallucination and persecutory delusion. He attempted to commit suicide by wrist cutting.

He had history of mild mental retardation and was first known to the Mental Health Services in his childhood. He had repeated admissions to mental hospital in relation to his repeated aggression and suicidal attempts driven by his psychotic symptoms. He was diagnosed to have paranoid schizophrenia on top of his mild mental retardation. Physically, he has history of allergy to seafood.

Concerning his medication history, he had been put on various psychiatric medications including chlorpromazine, trifluoperazine, zuclopenthixol depot, haloperidol, lithium carbonate, carbamazepine, sodium valproate, clonazepam, risperidone, olanzepine and clozapine for the control of his psychotic symptoms. However, he showed marked extra pyramidal reaction towards haloperidol. He also developed significant muscle rigidity while he was put on risperidone 3mg twice daily. He developed generalised tonic clonic convulsion and sinus tachycardia as he was put on clozapine 100mg in the morning and 175mg at night. Quetiapine was used instead of clozapine because of the marked and significant side effects that he suffered. He was started on Quetiapine 50mg daily and escalated the dose up to 150mg daily within two weeks. He developed fever (37.7°C) on Day 14. His blood pressure ranged from 140/100 to 100/60. Leukocyte count was 10.3 x 10⁹/L, alkaline phosphate of 61 U/L, ALT of 22 U/L, creatine kinase of 1680 U/L. He also showed muscle rigidity. Medication was stopped. Supportive treatment, anti-pyretics and diazepam 5mg twice daily was given. However, his fever went up to 38.5°C on Day 3 after the cessation of quetiapine. His blood pressure was labile and fluctuating. Electrocardiogram showed sinus tachycardia up to 132 beats in one minute. Chest radiography was unremarkable. Investigation showed leukocytes of 10.8 x 10⁹/L, alkaline phosphate of 62 U/L, ALT of 57 U/L, creatine kinase of 5101 U/L. A diagnosis of NMS was made. Anti-pyretics and intravenous fluid was given together with close monitoring. Treatment with dantrolene, and dopamine agonist was not used. Fever subsided and his blood pressure was normalised. Investigation revealed leukocyte of 5.9 x 10⁹/L, alkaline phosphate of 56 U/L, ALT of 15 U/L, creatine kinase of 176 U/L on Day 6 after the discontinuation of quetiapine. No more rigidity was observed. His vital signs including body temperature, pulse and blood pressure remained stable.

Discussion
Neuroleptic malignant syndrome is a fatal complication related to neuroleptic drug use. It is described as an idiosyncratic reaction to neuroleptic medications. NMS is assumed to be precipitated by central dopaminergic blockade. The ability of neuroleptic drugs to precipitate NMS appears to be related to their antidopaminergic potency (So 2001). There is no evidence between the actual dose or duration of exposure of the neuroleptic drug and the development of NMS. There is no significant difference in the duration of clinical symptoms with short-acting compared with long-acting
neuroleptic drugs (Shalev et al, 1989). The incidence of NMS syndrome is ranged from 0.2% (Caroff et al, 1993) to 2.2% (Hermesh et al, 1992). It occurs in all ages and is most prevalent in the male sex with the ratio of 2 to 1. Risk factors include male sex, young age, preceding agitation or exhaustion, dehydration, rapid increases in dosage of neuroleptics, pre-existing catatonia, past history of NMS (Caroff et al, 1993), and lower serum iron level (Rosebush et al, 1991). Medications associated with NMS including neuroleptic agents particularly those with D₂ blockade, atypical antipsychotics, anstiemetics, symptoms (Shalev & Munitz, 1986). Investigation pyramidal symptoms usually precede autonomic instability soon after the use of neuroleptic medications. Signs include catatonia, tachycardia, tachypnoea, labile blood pressure, dysarthria, dysphagia, sialorrhoea, rigidity, myoclonus (Caroff et al, 1993). There is no typical sequence of symptoms, but extra pyramidal symptoms usually precede autonomic symptoms (Shalev & Munitz, 1986). Investigation showed an elevation of serum creatine kinase, lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase (Caroff et al, 1993). There may be generalised slowing consistent with encephalopathy in electroencephalogram. Fever could have a central and a presynaptic origin. Heat is produced from serotonin stimulation in the thermoregulatory centre of the preoptic nuclei of the anterior hypothalamus. The dopaminergic receptor blockade reduces the inhibition of serotonin stimulation resulting in increases in heat production (Myers 1990). Moreover, dopamine may increase skeletal muscle contraction resulting in heat production and rigidity (Tollefson 1982). The autonomic instability in NMS is related to the hyperactivity of sympatho-adrenomedullary system. The increase in muscle tone and muscle rigidity is related to the dopaminergic blockade in the corpus striatum whereas the frontal-limbic involvement may lead to alteration of consciousness (Ebadi et al, 1990). Differential diagnosis include malignant hyperthermia, serotonin syndrome, lethal catatonia, and environmental heat disorder.

NMS usually develops within the first week of initiating neuroleptics and nearly all develop within the first month (Caroff et al, 1988). It is usually self-limiting after the cessation of neuroleptic agents. More than half of them improve after one week and nearly all of them recover after one month (Caroff et al, 1988). Conditions will be prolonged in those receiving depot neuroleptics. However, residual catatonic symptoms could persist for months if left untreated after the acute hyperthermic symptom subsides (Caroff et al, 2000). It could run a downhill course with rapid deterioration and the mortality rate is 20 to 30% (Shalev et al, 1989). The mortality rate for adolescents and prepubertal youths is 13% and 27% respectively (Peterson et al, 1995). Death may result from unexpected cardiopulmonary arrest, aspiration pneumonia, pulmonary emboli, myoglobinuric renal failure, or disseminated intravascular coagulation. Renal failure is a strong predictor of death, with an associated mortality of 50% (Adnet 2000).

Early recognition and prompt management are essential and could substantially reduce mortality and morbidity. NMS usually resolves after discontinuation the indexing agent together with supportive medical and nursing care (Caroff et al, 1993). Dopamine agonists including bromocriptine may be used to reverse the dopamine D₂ receptor blockade produced by neuroleptics. It could reduce muscle rigidity within a short time with associated reduction in temperature. Skeletal muscle relaxants like dantrolene could stimulate muscle relaxation by inhibiting ionised calcium release from sacroplasmic reticulum to relieve the muscle rigidity. Benzodiazepines could be an alternative to reduce muscle rigidity. Temperature could be reduced by means of anti-pyretics, ice pack, and cooling blankets. Alkalisation of urine and correction of volume depletion is necessary in case rhabdomyolysis occurs. ECT is shown to be effective in the treatment of severe NMS (Trollor et al, 1999).

Quetiapine is one of the atypical neuroleptic medications with different pharmacokinetic properties to the traditional ones. It has a low affinity for D₁, D₂ and 5HT₂ receptors but with moderate affinity for adrenergic α₁ and α₂ receptors. Based on its characteristics in receptor binding and the mechanism of NMS, it makes quetiapine uncommon to develop NMS and extra pyramidal side effects.

As illustrated by our case, he has a number of risk factors making him more vulnerable to develop NMS including young age, male sex, preceding agitation and exhaustion, recent change of neuroleptic medication and past history of severe extra pyramidal reaction towards traditional antipsychotic agents. Although the incidence of NMS was said to be lower reaction towards traditional antipsychotic agents. Previous reports showed NMS could happen after treatment with other atypical antipsychotic agents like risperidone, olanzapine (Stanfield & Privette 2000) and clozapine. Therefore, we need to pay more attention and alert oneself with the possibility of NMS if patient presented with rigidity, fever, autonomic instability and alteration of conscious level.

Conclusion

Neuroleptic malignant syndrome is a rare but potentially fatal complication induced by antipsychotic agents with potent dopaminergic blocking properties. Quetiapine with its predominantly blocking effect on adrenergic receptors, it is commonly believed that quetiapine rarely induces NMS. Therefore, we need to think of NMS for those who present with hyperthermia, muscle rigidity, altered consciousness and autonomic instability. Early diagnosis and treatment improves both morbidity and mortality.
References